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Imazethapyr. New Chemical Registration

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred:

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors

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b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

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Office of Pesticides and Toxic Substances
Office of Pesticide Programs (TS-766C)
Washington, DC 20460

540/FS-89-038

EPA

Pesticide Fact Sheet

Name of Chemical: Imazethapyr
Reason for Issuance:
Date Issued: March 8, 1989 (New Chemical Registration)
Fact Sheet Number: 196

1. Description of Chemical

Common Name: Imazethapyr
Chemical Name: (+)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-ethyl-3-pyridinecarboxylic acid
Trade Name: Pursuit®
OPP (Shaughnessy) No.: 128982
Chemical Abstracts Services (CAS) Number:
Empirical Formula: $C_{15}H_{22}N_4O_3$
Molecular Weight: 306.4
Year of Initial Registration: 1989
Pesticide Type: Herbicide
U.S. Producer: American Cyanamid Company

2. Use Patterns and Formulations

Application Sites: Terrestrial food crops

Major Crops Treated: Soybeans

Types and Methods of Application: Foliar or soil, applied broadcast by ground equipment for control of broadleaf weeds and grasses. Applied early preplant, preplant incorporated, preemergence, or early postemergence.

Application Rate: 0.0625 pounds active ingredient/acre (lb ai/A) or 4 ounces product/A.

Type of Formulations: Emulsifiable concentrate.

Usual Carriers: Water with crop oil or a nonionic surfactant.

3. Science Findings

Summary Science Statement: All data are acceptable. Imazethapyr has low acute toxicity (Category III) for acute dermal, primary eye irritation, and acute inhalation and is less toxic (Category IV)

for acute oral toxicity and primary dermal irritation. Imazethapyr is not considered a skin sensitizer. Data does not show imazethapyr to be oncogenic in rats or mice. The chemical is not teratogenic in rats or rabbits, and did not produce any reproductive effects in rats. Imazethapyr is not considered mutagenic except at levels toxic to cells.

Imazethapyr is practically nontoxic to birds, fish, aquatic vertebrates, and honey bees.

Imazethapyr is persistent regardless of soil type, agricultural practices, and climatic effects but does not appear to leach under normal soybean agricultural practices.

The nature of the residue in plants and animals is adequately understood and adequate methodology is available for enforcement of the tolerance in soybeans.

Chemical Characteristics:

Technical

Physical State: Solid
Color: Off-white to tan
Odor: Pungent
Boiling Point: N/A
Density: 0.396 g/mL untapped, 0.459 g/mL tapped
Solubility:

Solvent	Solubility at 25 °C (g/100 mL Solvent)
Acetone	4.82
Dimethyl sulfoxide	42.25
Heptane	0.09
Methanol	10.50
Methylene chloride	18.48
2-Propanol	1.73
Toluene	0.50
Water (distilled)	0.14

Vapor Pressure: (pure form) $< 1 \times 10^{-7}$ mm Hg at 60 °C
Dissociation Constant: pka = 3.9
pH: 2.85 at 25 °C

Toxicology Characteristics:

Acute Toxicology - Technical

- Acute Oral Toxicity - Rat: > 5000 mg/kg/day (male and females)
  Toxicity Category IV

- o Acute Dermal Toxicity - Rabbit: > 5000 mg/kg/day (males and females) Toxicity Category III

- o Primary Dermal Irritation - Rabbit: Imazethapyr is minimally irritating. Toxicity Category IV

- o Primary Eye Irritation: Imazethapyr is practically nonirritating. Toxicity Category III

- o Dermal Sensitization - Guinea Pig: Imazethapyr is not a dermal sensitizer

- o Acute Inhalation: > 3.27 mg/L air (analytical) or 4.21 mg/L air (gravimetric). Toxicity Category III

Acute Toxicology - Pursuit Herbicide (22.6% Formulation)

- o Acute Oral Toxicity - Rat: > 5000 mg/kg (males and females) Toxicity Category IV

- o Acute Dermal Toxicity - Rabbit: > 5000 mg/kg (males and females) Toxicity Category IV

- o Primary Eye Irritation - Rabbit: minimally irritating Toxicity Category IV

- o Primary Dermal Irritation: Minimally irritating Toxicity Category IV

Acute Toxicology - Pursuit Plus (2.39% Formulation)

- o Acute Oral Toxicity - Rat: > 5000 mg/kg (males and females) Toxicity Category IV

- o Acute Dermal Toxicity - Rats: > 2000 mg/kg (males and females) Toxicity Category III

- o Acute Inhalation Toxicity - LC_{50} (males and females) 1.29 mg/ imazethapyr and 1.27 mg/pendimethalin. Toxicity Category III

- o Primary Eye Irritation - Rabbits: Slight irritation at 24 hours Toxicity Category III

- o Primary Dermal Irritation - Rabbits: No erythema or edema observed. Toxicity Category IV

- o Dermal Sensitization - Guinea Pig: not a sensitizer

Subchronic Toxicity

Data are available to satisfy the requirements for sub chronic feeding studies. These data are discussed below.

A 90-day rat subchronic feeding study conducted at dose levels of 0, 1000, 5000, and 10,000 parts per million (ppm) (0, 50, 250, and 500 milligrams/kilogram [mg/kg]/day) resulted in a no-observable effect level (NOEL) of 500 mg/kg/day (highest does tested [HDT]).

A 90-day dog subchronic feeding study conducted at dosages of 0, 1000, 5000, and 10,000 ppm (0, 25, 125, and 250 mg/kg/day) resulted in a NOEL of 250 mg/kg/day (HDT).

A 21-day rabbit dermal study conducted at dosages of 0, 250, 500, and 1000 mg/kg/day resulted in a NOEL of 1000 mg/kg/day (HDT).

Chronic Feeding and Oncogenicity Studies

Data are available to satisfy the requirements for chronic feeding studies and oncogenicity studies in two species. These data are discussed below.

A dog chronic feeding study conducted at dosages of 0, 1000, 5000, and 10,000 ppm (0, 25, 125, and 250 mg/kg/day) resulted in a NOEL of 250 mg/kg/day (HDT) in males and a NOEL for females of 25 mg/kg/day. The lowest-observed-effect level (LOEL) of 125 mg/kg for females was based on decreased packed cell volume hemoglobin and erythrocytes at 250 mg/kg/day.

A 2-year rat chronic feeding/oncogenicity study conducted at dosages of 0, 1000, 5000, and 10,000 ppm (0, 50, 200, and 500 mg/kg) with no oncogenic effects observed up to 500 mg/kg/day (HDT). This study is acceptable as a chronic feeding study with a NOEL of 500 mg/kg/day (HDT) but is classified as Supplemental for an oncogenic study because the maximum tolerated dose (MTD) was not reached (no significant toxic effects at the HDT). A repeat of this study is not required at this time because 1) 500 mg/kg (10,000 ppm) is within 50 percent of the limit dose for an adequately conducted oncogenicity study on a chemical of low toxicity; 2) this pesticide is closely related to two other pesticides ("Scepter" and "Assert") which tested negatively in oncogenicity testing; and 3) there were no positive mutagenicity studies for any of the three pesticides except for "Pursuit," which had a positive result in the in vitro cytogenetics study, but only at levels that were toxic to the cells.

A 78-week mouse oncogenicity feeding study conducted at dosages of 0, 1000, 5000, and 10,000 ppm (0, 50, 750, and 1500 mg/kg/day) produced no oncogenic effects up to 1500 mg/kg/day (HDT). The systemic NOEL was 750 mg/kg/day based on decreased body weight gains in both sexes.

Justification that the highest dose level tested in the rat chronic feeding/oncogenicity study (1500 mg/kg) is sufficient or a new study with an MTD will be required for before additional crop tolerances or registrations can be issued.

Teratogenicity and Reproduction

Data are available to satisfy the requirements for a 2-generation reproduction study and teratology studies in two species. These studies are discussed below.

A rat teratology study conducted at dosages of 0, 125, 375, or 1125 mg/kg/day demonstrated an NOEL for developmental toxicity of 1125 mg/kg/day (HDT). The NOEL for maternal toxicity was 375 mg/kg/day and the LOEl was 1125 mg/kg/day (HDT).

A rabbit teratology study was calculated at dosages of 0, 100, 300, or 1000 mg/kg/day showed no teratogenic effects observed. The NOEL for maternal toxicity was 300 mg/kg/day and the NOEL for developmental (embryo/fetotoxicity was 1000 mg/kg/day (HDT)).

A 2-generation rat reproduction study conducted at dosages of 0, 1000, 5000, and 10,000 ppm (0, 50, 200, and 500 mg/kg). The systemic and reproductive NOEL was 500 mg/kg/day. The study is classified as supplementary because the dose levels were not high enough. A repeat study is not required because it would not likely provide any useful information since the chronic dog study would still be the preferred study.

Mutagenicity

Acceptable data are available for imazethapyr to satisfy the mutagenicity data requirements. These data are discussed below.

Data available to evaluate the potential of imazethapyr to induce gene mutations include reverse mutation assays in S. typhimurium and E. coli, both plate and disc tests. Imazethapyr did not induce gene mutation in either system up to 5000 micrograms (ug)/plate or 1000 ug per disc. Imazethapyr was also tested in a Chinese Hamster Ovary (CHO) cell gene mutation assay (HGPRT locus) up to the limit

of solubility with activation (3333 ug/mL) and beyond the limit of solubility without activation (4000 ug/mL). Imazethapyr did not induce gene mutation in this system.

Imazethapyr did not result in a significant increase in chromosomal aberrations in rat bone marrow when tested in an acute in vivo cytogenics assay at dose levels of 0.25, 0.8, and 2.5 grams (g)/kg body weight. When tested in an in vitro cytogenics assay in CHO cells both with and without metabolic activation at dosage levels of 1.14, 1.71, 1.82, 2.05, and 2.25 mg/mL imazethapyr increased chromosomal aberrations without metabolic activation at dosage levels toxic to cells and did not increase chromosomal aberrations with metabolic activation. Imazethapyr was also tested in a dominant lethal rat study at dose levels of 0, 200, 1000, or 2000 mg active ingredient (ai)/kg and did not induce dominant lethal mutations. This study is Supplemental because it was questionable whether or not dose levels were high enough for an adequate negative study. Another study is not required because the other studies satisfy this requirement.

Data available to evaluate the potential of imazethapyr to induce DNA damage includes an in vitro unscheduled DNA synthesis study in primary rat hepatocytes tested at dose levels ranging from 13 to 1333 ug/well. Under the conditions of this test, imazethapyr did not induce unscheduled DNA synthesis in rat hepatocytes.

Metabolism

Two rat metabolism studies were conducted. These studies do not completely characterize the absorption, excretion, retention, and metabolism of imazethapyr. However, a repeat study is not necessary for this use because currently available data give sufficient evidence that most of the chemical will be eliminated via the urine unchanged.

Physiological and Biochemical Characteristics

Translocation and absorption by plants: Absorption through both roots and foliage and translocated rapidly to growing points.

Metabolism/persistence in animals: Eliminated through the urine unchanged.

Environmental Characteristics

Leaching and Adsorption/Desorption: Laboratory studies show imazethapyr to be very mobile in two sand loam and two silt loam soils. The percentage of organic matter and sand do not appear to have an effect on the sorption of imazethapyr.

Field dissipation tests were conducted using preplant incorporation, pre- and postemergence applications. Fields were planted to soybeans. Irrigation was not used because irrigation is not a normal agricultural practice for soybeans. In Kentucky silt loam, imazethapyr was detected at the 0- to 3-inch depth in all methods of application. Half-lives of 31 days for preplant incorporated, 20 days for preemergence, and 17 days for postemergence were calculated. At one sampling for both preemergence and preplant incorporated methods of application, imazethapyr was detected at the 3- to 6-inch depth. Imazethapyr was not detected at other sampling intervals in 3- to 6-inch depths or at 6- to 9- and 9- to 12-inch sampling depths. These plots did not indicate leaching.

In an Illinois silt loam soil, residues of imazethapyr were detected in the 0- to 3-inch depth for all types of application. Concentrations of imazethapyr detected between 30 and 60 days at the 3- to 6-inch depth and persisted until the end of the study when imazethapyr was applied preplant incorporated. The half-life was calculated to be 287 days. When applied pre- and postemergence, imazethapyr was not detected below the 0- to 3-inch depth. The half-life was calculated to be 120 days.

In coarse, sandy soils found in some soils in Georgia and Iowa, movement to 12 inches was noted. Further soil dissipation studies will be needed for future uses with agricultural practices different from soybeans and in soil types similar to soils found in Georgia and Iowa.

Microbial breakdown: Imazethapyr degrades slowly under aerobic (half-life of 33 to 37 months) conditions and very slowly under anaerobic conditions.

Loss from volatilization: None expected because of low vapor pressure.

Degradation from photodecomposition and hydrolysis: Imazethapyr is stable to hydrolysis at pHs 5, 7, 9 in buffered or pond water. Imazethapyr is resistant to degradation in soil when exposed to artificially simulated sunlight. Imazethapyr degrades when exposed to artificially simulated sunlight with a half-life of 46 hours.

Bioaccumulation fish: Does not bioaccumulate in fish.

Potential to contaminate groundwater: Imazethapyr is persistent and mobile as indicated from laboratory studies. In the field, imazethapyr consistently shows persistence, regardless of soil type, agricultural practices, and climatic effects. In the field, imazethapyr does not leach to the same extent in all soil types

and under all agricultural practices. Based on field dissipation studies performed on soils planted to soybeans under normal agricultural practices (no irrigation) imazethapyr does not appear to leach. Therefore, the potential to contaminate groundwater from use on soybeans is low.

Exposure of humans to pesticides and reentry: Applicator exposure assessment or reentry exposure are not required because lack of significant chronic concerns and low acute toxicity (Category III and IV) result in low exposure to humans from imazethapyr.

Based on available information, only the minimal reentry intervals required by law should be imposed at this time: Entry into treated fields shall not be permitted without protective clothing until sprays have dried and dusts have settled.

Ecological Characteristics

Acceptable data are available to satisfy the requirements for an avian single dose acute oral toxicity on one species; two subacute dietary toxicity studies on one species of waterfowl and one species of upland gamebird; two 96-hour fish acute toxicity studies on two species of freshwater fish, preferably one coldwater species and one warmwater species; a 48-hour acute toxicity study with freshwater invertebrates; and an acute oral toxicity to honey bees. Studies that satisfy these requirements are listed below.

- o Avian Acute Toxicity: Bobwhite Quail LC_{50} > 2150 mg/kg and Mallard Duck LC_{50} > 2150 mg/kg
- o Avian Dietary Toxicity: Mallard Duck LC_{50} > 5000 mg/kg and Bobwhite Quail LC_{50} > 5000 mg/kg
- o Freshwater Fish Acute Toxicity: Channel Catfish LC_{50} 240 mg/L, Bluegill Sunfish LC_{50} 420 mg/L, and Rainbow Trout LC_{50} 340 mg/L
- o Freshwater Invertebrate Toxicity: Daphnia magna LC_{50} > 1000 mg/L
- o Acute Contact Toxicity: Honey bee LC_{50} > 1000 ug/bee

Based on the above data, imazethapyr is practically nontoxic to birds on an acute and dietary basis, practically nontoxic to both warmwater and coldwater fish, practically nontoxic to aquatic invertebrates, and practically nontoxic to honey bees.

Tolerance Assessment:

The nature of the residue in plants and animals has been adequately defined for the use on soybeans and adequate analytical methods are available for enforcement purposes.

A tolerance is established for residues of the herbicide imazethapyr, ammonium salt, (+)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-ethyl-3-pyridinecarboxylic acid) in or on the raw agricultural commodity soybeans at 0.1 ppm.

The PADI was calculated to be 0.25 mg/kg/day. This value was based on a NOEL of 250 mg/kg/day from the 90-day dog feeding study. An uncertainty factor of 1000 was used because an MTD was not obtained in the rat chronic/ oncogenicity study.

The theoretical maximum residue contribution (TMRC) from this tolerance is calculated to be 0.000034 mg/kg/body weight/day which occupies approximately 0.014 percent of the PADI. There are no other published tolerances for this chemical.

4. Summary of Regulatory Position and Rationale

The available data submitted to the Agency provide sufficient information to support registration of the use on soybeans. Therefore, the Agency has accepted the use of imazethapyr on soybeans.

5. Data Gaps

There are no data gaps for the use of imazethapry on soybeans.

6. Contact Person at EPA

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